

To: Jack Kennealy and Ilse Light, ONCOR  
 From: Gerard Nuovo, MGN Medical Consultants  
 Re: HPV *in situ* study  
 Date:

Dear Jack and Ilse:

I would like to summarize the data/findings that relate to the different issues we discussed recently:

- ◊ HPV 42, 43, and 44 data. This is summarized in the tables included with this letter. It is clear from this data that high copy HPV 6/11,42,43,or 44 positive cases can cross hybridize with the "high risk" ONCOR probe cocktail (each at 500 ng/ml) at low stringency (1XSSC, 2% BSA, and 45°C for 5 min). Our options are to increase the stringency and/or decrease the concentration of the various probes. To do the latter, we must know the hybridization profiles of the different HPV types.
- ◊ Cross hybridization profiles of the different HPV types. I performed *in situ* hybridization using 500 ng/ml of the ONCOR probe cocktails with tissues known to contain a variety of HPV types. The data follows:

Cross hybridization patterns\*

	HPV 16	HPV 18	HPV 31	HPV 33	HPV 35	HPV 51
6/11	2+	0	1+	0	weak	0
18	0	3+	0	0	0	
45	0	2+	0	weak	0	0
52	0	0	0	0	2+	0
56	1+	0	1+	0	weak	0

\* Done at low stringency.

- ◊ With this information, we did two sets of experiments:
  - (a) High stringency wash;
  - (b) Relationship of signal for HPV 6/11+ case with different concentrations of HPV 16 probes. I chose HPV 16, of course, because it is the one most responsible for the signal with the HPV 6/11 tissues. The data follow:

### SIGNAL INTENSITY Varying stringency

Case	HPV type	specific HPV type	Digene Omniprobe	ONCOR consensus
5	6/11	Low stringency*		
		3+ (Digene)	3+	2+
5	6/11	High stringency*		
		3+ (Digene)	3+	0
17	56	Low stringency		
		3+ (Digene)	3+	3+
17	56	High stringency		
		3+ (Digene)	3+	0

\* Low stringency = 5 minutes at 45°C in 1XSSC and 2% BSA

\*High stringency = 10 minutes at 62°C in 0.1XSSC and 2% BSA

Obviously, the high stringent conditions eliminate the signal with the HPV 6/11 tissue but also cause us to lose the signal with an important "novel" type - HPV 56.

The next strategy was to see if we could eliminate the signal with the HPV 6/11 tissue at low stringency using a lower concentration of the "culprit" HPV 16. The data follows:

### HPV 16 concentration study

	500 ng/ml	200 ng/ml	100 ng/ml	50 ng/ml	33 ng/ml	25 ng/ml
6/11 hi*	2+	weak	0	0	0	0
16 hi*	3+	3+	2+	weak	weak	weak
16 low*	1+	1+	1+	0	0	0

\* The HPV 6/11 tissue was a cervical low grade SIL with strongest signal I have ever seen. Of course, this was done because if we can eliminate the signal with it, then lower copy HPV 6/11 tissues will also be scored as negative.

In summary, it is clear that a concentration for HPV 16 in the probe cocktail of 100-200 ng/ml should greatly facilitate eliminating the HPV 6/11 cross over.

◊ True blue reagent and hybrisol. I used the hybrisol and true blue for the data just reported. Clearly, these work very well.

- ◊ Novel types (specifically HPV 39,58,59, and 68). My assistant and I are beginning the experiments using PCR to identify and type new HPVs based on the published endonuclease profiles. I've included in this report a paper which describes the identification of HPV 70. As you can see from the abstract, this type strongly cross reacts with HPV 39,59, and 68. Clearly, if HPV 70 could be included in the ONCOR cocktail, this should permit detection of these types. Hopefully, I will find HPV 70 in my collection. A quick and simple way to enhance the ONCOR system is to prepare several oligos of 40-50 bp from the HPV 70 sequence and include this in the cocktail.
- ◊ Hybrid capture system. I'll briefly review this information, as it was discussed in my recent Email. The Hybrid capture system is done at high stringency, and one must use >4,000 pg of HPV 6/11 to see a signal with the high risk cocktail. Most HPV 6/11 cervical warts would not have such a high copy number. I think the key to stress is that the ONCOR system is superior to the Hybrid capture system in several ways:
  - ⇒ It detects clinical infection whereas the Digene system also detects subclinical infection;
  - ⇒ Because it is done at low stringency, it can detect a greater range of novel high risk HPV types and still avoid detecting the low risk types by using the correct proportion of HPV types in the cocktail;
  - ⇒ The ONCOR system allows the pathologist to identify the infected cell type (ASCUS, dysplasia, eg) whereas the Digene system does not.

## SUMMARY

- \* The key data is the cross hybridization of HPV 6/11 with the high risk types and the realization that we can eliminate the HPV 6/11 signal by adjusting the concentration of the HPV 16 probe and still maintain low stringent conditions.
- \* The ONCOR system as it stands now does an excellent job in detecting the "still novel" types (ie, not HPVs 16,18,31,33,35,45,51,52, or 56); these must include HPVs 39,58,59, and 68. It hasn't missed one yet! We should maintain low stringency to continue to make this a selling point of the ONCOR system. The high stringency Digene hybrid capture system can't detect these novel types; this is why they are adding yet more types. The inclusion of HPV 70 (all or part) should allow the ONCOR system to perform even better with most of these "still novel" HPV types.
- \* If we go to high stringency, we will lose the signal of many of these novel types unless we get probes for all or most of them. Although I'll try to isolate

these novel types, I don't think the ONCOR system needs them to be successful whereas the Digene system does need them.

**SIGNAL INTENSITY**  
**High risk types**  
**Low stringency**

Case	HPV type	specific HPV type*	Digene Omniprobe	ONCOR consensus
1	16	3+	2+	3+
2	16	weak	1+	1+
3	16	2+	2+	2+
4	16	2+	2+	2+
5	18	3+	1+	3+
6	18	3+	3+	3+
7	31	3+	1+	3+
8	33	3+	3+	3+
9	33	3+	3+	3+
10	35	3+	3+	3+
11	45	3+ (digene)	3+	3+
12	45	2+ (digene)	2+	2+
13	51	2+	2+	2+
14	51	1+	1+	1+
15	52	2+ (digene)	2+	1+
16	52	3+ (digene)	3+	2+
17	56	3+ (digene)	2+	2+
18	56	3+ (digene)	3+	3+
19	novel, 45R	45 = 3+	3+	1+
20	novel, 35R	35 = 1+	1+	1+
21	novel, many types	6,16,31/33/35+	3+	3+
22	novel, 16R	1+ (digene)	1+	1+

\* The specific HPV type is from the genomic ONCOR probe except for HPV types 45, 52, novel types, and 56 where the Digene probe was used.  
 The signal intensity varied from 1+ (weak signal, light blue), 2+ (moderate signal, blue), and 3+ (intense signal, blue-black).

**SIGNAL INTENSITY****Low risk types****Low stringency**

Case	HPV type	specific HPV type	Digene Omniprobe	ONCOR consensus
1	6/11	3+ (Digene)	3+	1+
2	6/11	2+ (Digene)	2+	0
3	6/11	2+ (Digene)	2+	0
4	6/11	1+ (Digene)	1+	0
5	6/11	3+ (Digene)	3+	2+
6	6/11	2+ (Digene)	2+	0
7	42	2+ (Digene)	2+	0
8	43	1+ (Digene)	1+	0
9	44	3+ (Digene)	3+	1+

**NEW DATA**  
**ONCOR consensus probe cocktail data**  
**Low stringency**

	Digene probe*	Cocktail 1**	Cocktail 2	Cocktail 3
2	0 (3+ HPV 2)	0	0	0
6/11	3+	2+	0	0
6/11	3+	2+	1+	weak
6/11	3+	1+	0	0
6/11	3+	3+	0	0
6/11	2+	1+	0	0
6/11	1+	0	0	0
6/11	3+	1+	0	0
6/11	1+	0	0	0
6/11	3+	1+	0	0
42	2+	ND	0	0
43	2+	ND	0	0
44	2+	0	0	0
16	1+	1+	1+	1+
16	3+	3+	3+	2+
16	3+	3+	3+	3+
16	2+	2+	2+	1+
16	1+	1+	1+	1+
18	3+	3+	3+	3+
31	2+	2+	2+	2+
31	3+	3+	3+	3+
31	3+	3+	3+	3+
33	3+	3+	3+	3+
45	3+	3+	3+	3+
56	3+	2+	2+	1+
56	3+	2+	1+	1+
still novel	3+ (45 related)	3+	3+	2+
	2+ (16 related)	2+	1+	1+

\* The digene probe is their type specific probe.

\*\* Cocktail 1 has 500 ng/ml of HPV 16, cocktail 2 has 200 ng/ml HPV 16, and cocktail 3 has 100 ng/ml. Each cocktail has 500 ng/ml of HPVs 18,33,35, and 51 plus 200 ng/ml of HPV 31.

To: Jack Kennealy, PhD and Ilse Light  
From: Gerard Nuovo  
Re: HPV testing  
Date:

Dear Ilse and Jack:

I am sending some more information with regards to HPVs 45,52, and 56. As you can see, HPV 56 can be detected by HPV 31, HPV 52 is most related to HPV 33, and HPV 45 is most related to HPV 18. You may recall that HPV 31 did detect HPV 56 and HPV 18 did detect HPV 45 when I did these tests using the individual ONCOR genomic probes. The fact that HPVs 31,33, and 18 are in the ONCOR consensus probe cocktail at 500 ng/ml explains why we are detecting these types readily at low stringency. We are a bit lucky that HPV 16, which is causing most of the cross over with HPVs 6/11, appears to be less important in detecting the "novel" types (ie, HPVs 45,52,56), and the "still novel" types of HPVs 39,58,59, and 68.

I look forward to talking with you on Friday.  
Sincerely,

Gerard Nuovo, MD

## SUMMARY OF PREVIOUS DATA

**HPV 16 concentration study**

	500 ng/ml	200 ng/ml	100 ng/ml	50 ng/ml	33 ng/ml	25 ng/ml
6/11 hi*	2+	weak	0	0	0	0
16 hi*	3+	3+	2+	weak	weak	weak
16 low*	1+	1+	1+	0	0	0

\* The HPV 6/11 tissue was a cervical low grade SIL with strongest signal I have ever seen. Of course, this was done because if we can eliminate the signal with it, then lower copy HPV 6/11 tissues will also be scored as negative.

SUMMARY OF PREVIOUS DATA  
**Detection frequencies of the different HPV types**

	500 ng/ml	200 ng/ml	100 ng/ml	50 ng/ml	33 ng/ml	25 ng/ml
6/11 hi*	2+	weak	0	0	0	0
16 hi*	3+	3+	2+	weak	weak	weak
16 low*	1+	1+	1+	0	0	0

\* The HPV 6/11 tissue was a cervical low grade SIL with strongest signal I have ever seen. Of course, this was done because if we can eliminate the signal with it, then lower copy HPV 6/11 tissues will also be scored as negative.

\* The Eligen probe is their type specific probe

\*\* Cocktail 1 has 500 ng/ml of HPV 18, cocktail 2 has 200 ng/ml HPV 16, and cocktail 3 has 100 ng/ml. Each cocktail has 200 ng/ml of HPV's 18,33,31, and 31 plus 200 ng/ml of HPV 31.

To: Jack Kennealy, PhD and Ilse Light  
FAX: 301-963-1436  
From: Gerard Nuovo  
Re: HPV testing  
Date:

Dear Ilse and Jack:

I am re-sending the FAX of . Also included with this FAX is an update on the ONCOR probe study; note that I have included HPV 52 and another still novel type.

I look forward to talking with you at 300.  
Sincerely,

Gerard Nuovo, MD

NEW DATA (n = 57)  
 ONCOR consensus probe cocktail data  
 Low stringency

	Digene probe*	Cocktail 1**	Cocktail 2	Cocktail 3
2	0 (3+ HPV 2)	0	0	0
6/11	1+	0	0	0
6/11	1+	0	0	0
6/11	2+	1+	0	0
6/11	3+	2+	0	0
6/11	3+	2+	1+	weak
6/11	3+	1+	0	0
6/11	3+	3+	0	0
6/11	3+	1+	0	0
6/11	3+	1+	0	0
6/11	1+	0	0	0
6/11	1+	0	0	0
42	2+	-	0	0
43	2+	-	0	0
44	2+	0	0	0
16	1+	1+	1+	1+
16	1+	1+	1+	1+
16	2+	2+	2+	1+
16	wcsak	1+	1+	1+
16	3+	3+	3+	2+
16	3+	3+	3+	3+
18	3+	3+	3+	3+
31	2+	2+	2+	2+
31	3+	3+	3+	3+
31	3+	3+	3+	3+
33	3+	3+	3+	3+
33	2+	2+	2+	2+
35	3+	3+	3+	3+
35	1+	-	-	1+
51	3+	3+	3+	3+
30	3+	3+	3+	3+
30	3+	3+	3+	3+
30	3+	3+	3+	3+
39	2+	1+	1+	1+
39	2+	2+	2+	2+
39	1+	weak	wcsak	weak
39	3+	3+	3+	3+
39	3+	-	3+	3+
39	1+	1+	1+	1+
45	3+	3+	3+	3+
45	3+	-	3+	3+
52	3+	3+	3+	3+
52	3+	3+	3+	3+
52	2+	2+	2+	2+
56	3+	3+	3+	3+
56	1+	1+	1+	1+
56	3+	2+	2+	1+
56	3+	2+	1+	1+
58	2+	2+	1+	1+
59	2+	2+	2+	-
68	1+	-	1+	1+
70	3+	3+	3+	2+
70	2+	ND	2+	-
70	1+	1+	1+	1+
still novel	2+ (31 related)	2+	2+	2+
	1+ (18 related)	1+	1+	1+
	1+ (18 related)	1+	1+	1+

Cross homology patterns\*  
 Gerard Nuovo, MD  
 MCN Medical Research Laboratories

TABLE 2.

	HPV 16	HPV 18	HPV 31	HPV 33	HPV 35	HPV 51	HPV 70	HPV 61
611	0	0	0	0	0	0	0	3+
16	3+	0	0	0	0	0	0	0
18	0	3+	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0
31	weak	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0
41	0	0	1+	0	0	0	0	0
43	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0
56	1+	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0
59	0	1+	0	0	0	0	0	0
68	0	1+	0	0	0	0	0	0
70	0	1+	0	0	0	0	0	0

\* Done at high stringency (60°C in 0.2XSSC and 2% bovine serum albumin for 10 min) using tissues/Pap smears known to contain the different HPV types listed in the Table. Concentration of each probe at 500 ng/ml.

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Cocktail 1**		Cocktail 2		Cocktail 3		Cocktail 4	
Sample	Time	Sample	Time	Sample	Time	Sample	Time
1	0	1	0	1	0	1	0
2	10	2	10	2	10	2	10
3	20	3	20	3	20	3	20
4	30	4	30	4	30	4	30
5	40	5	40	5	40	5	40
6	50	6	50	6	50	6	50
7	60	7	60	7	60	7	60
8	70	8	70	8	70	8	70
9	80	9	80	9	80	9	80
10	90	10	90	10	90	10	90
11	100	11	100	11	100	11	100
12	110	13	110	13	110	13	110
14	120	15	120	15	120	15	120
16	130	17	130	17	130	17	130
18	140	19	140	19	140	19	140
20	150	21	150	21	150	21	150
22	160	23	160	23	160	23	160
24	170	25	170	25	170	25	170
26	180	27	180	27	180	27	180
28	190	29	190	29	190	29	190
30	200	31	200	31	200	31	200
32	210	33	210	33	210	33	210
34	220	35	220	35	220	35	220
36	230	37	230	37	230	37	230
38	240	39	240	39	240	39	240
40	250	41	250	41	250	41	250
42	260	43	260	43	260	43	260
44	270	45	270	45	270	45	270
46	280	47	280	47	280	47	280
48	290	49	290	49	290	49	290
50	300	51	300	51	300	51	300
52	310	53	310	53	310	53	310
54	320	55	320	55	320	55	320
56	330	57	330	57	330	57	330
58	340	59	340	59	340	59	340
60	350	61	350	61	350	61	350
62	360	63	360	63	360	63	360
64	370	65	370	65	370	65	370
66	380	67	380	67	380	67	380
68	390	69	390	69	390	69	390
70	400	71	400	71	400	71	400
72	410	73	410	73	410	73	410
74	420	75	420	75	420	75	420
76	430	77	430	77	430	77	430
78	440	79	440	79	440	79	440
80	450	81	450	81	450	81	450
82	460	83	460	83	460	83	460
84	470	85	470	85	470	85	470
86	480	87	480	87	480	87	480
88	490	89	490	89	490	89	490
90	500	91	500	91	500	91	500
92	510	93	510	93	510	93	510
94	520	95	520	95	520	95	520
96	530	97	530	97	530	97	530
98	540	99	540	99	540	99	540
100	550	101	550	101	550	101	550
102	560	103	560	103	560	103	560
104	570	105	570	105	570	105	570
106	580	107	580	107	580	107	580
108	590	109	590	109	590	109	590
110	600	111	600	111	600	111	600
112	610	113	610	113	610	113	610
114	620	115	620	115	620	115	620
116	630	117	630	117	630	117	630
118	640	119	640	119	640	119	640
120	650	121	650	121	650	121	650
122	660	123	660	123	660	123	660
124	670	125	670	125	670	125	670
126	680	127	680	127	680	127	680
128	690	129	690	129	690	129	690
130	700	131	700	131	700	131	700
132	710	133	710	133	710	133	710
134	720	135	720	135	720	135	720
136	730	137	730	137	730	137	730
138	740	139	740	139	740	139	740
140	750	141	750	141	750	141	750
142	760	143	760	143	760	143	760
144	770	145	770	145	770	145	770
146	780	147	780	147	780	147	780
148	790	149	790	149	790	149	790
150	800	151	800	151	800	151	800
152	810	153	810	153	810	153	810
154	820	155	820	155	820	155	820
156	830	157	830	157	830	157	830
158	840	159	840	159	840	159	840
160	850	161	850	161	850	161	850
162	860	163	860	163	860	163	860
164	870	165	870	165	870	165	870
166	880	167	880	167	880	167	880
168	890	169	890	169	890	169	890
170	900	171	900	171	900	171	900
172	910	173	910	173	910	173	910
174	920	175	920	175	920	175	920
176	930	177	930	177	930	177	930
178	940	179	940	179	940	179	940
180	950	181	950	181	950	181	950
182	960	183	960	183	960	183	960
184	970	185	970	185	970	185	970
186	980	187	980	187	980	187	980
188	990	189	990	189	990	189	990
190	1000	191	1000	191	1000	191	1000
192	1010	193	1010	193	1010	193	1010
194	1020	195	1020	195	1020	195	1020
196	1030	197	1030	197	1030	197	1030
198	1040	199	1040	199	1040	199	1040
200	1050	201	1050	201	1050	201	1050
202	1060	203	1060	203	1060	203	1060
204	1070	205	1070	205	1070	205	1070
206	1080	207	1080	207	1080	207	1080
208	1090	209	1090	209	1090	209	1090
210	1100	211	1100	211	1100	211	1100
212	1110	213	1110	213	1110	213	1110
214	1120	215	1120	215	1120	215	1120
216	1130	217	1130	217	1130	217	1130
218	1140	219	1140	219	1140	219	1140
220	1150	221	1150	221	1150	221	1150
222	1160	223	1160	223	1160	223	1160
224	1170	225	1170	225	1170	225	1170
226	1180	227	1180	227	1180	227	1180
228	1190	229	1190	229	1190	229	1190
230	1200	231	1200	231	1200	231	1200
232	1210	233	1210	233	1210	233	1210
234	1220	235	1220	235	1220	235	1220
236	1230	237	1230	237	1230	237	1230
238	1240	239	1240	239	1240	239	1240
240	1250	241	1250	241	1250	241	1250
242	1260	243	1260	243	1260	243	1260
244	1270	245	1270	245	1270	245	1270
246	1280	247	1280	247	1280	247	1280
248	1290	249	1290	249	1290	249	1290
250	1300	251	1300	251	1300	251	1300
252	1310	253	1310	253	1310	253	1310
254	1320	255	1320	255	1320	255	1320
256	1330	257	1330	257	1330	257	1330
258	1340	259	1340	259	1340	259	1340
260	1350	261	1350	261	1350	261	1350
262	1360	263	1360	263	1360	263	1360
264	1370	265	1370	265	1370	265	1370
266	1380	267	1380	267	1380	267	1380
268	1390	269	1390	269	1390	269	1390
270	1400	271	1400	271	1400	271	1400
272	1410	273	1410	273	1410	273	1410
274	1420	275	1420	275	1420	275	1420
276	1430	277	1430	277	1430	277	1430
278	1440	279	1440	279	1440	279	1440
280	1450	281	1450	281	1450	281	1450
282	1460	283	1460	283	1460	283	1460
284	1470	285	1470	285	1470	285	1470
286	1480	287	1480	287	1480	287	1480
288	1490	289	1490	289	1490	289	1490
290	1500	291	1500	291	1500	291	1500
292	1510	293	1510	293	1510	293	1510
294	1520	295	1520	295	1520	295	1520
296	1530	297	1530	297	1530	297	1530
298	1540	299	1540	299	1540	299	1540
300	1550	301	1550	301	1550	301	1550
302	1560	303	1560	303	1560	303	1560
304	1570	305	1570	305	1570	305	1570
306	1580	307	1580	307	1580	307	1580
308	1590	309	1590	309	1590	309	1590
310	1600	311	1600	311	1600	311	1600
312	1610	313	1610	313	1610	313	1610
314	1620	315	1620	315	1620	315	1620
316	1630	317	1630	317	1630	317	1630
318	1640	319	1640	319	1640	319	1640
320	1650	321	1650	321	1650	321	1650
322	1660	323	1660	323	1660	323	1660
324	1670	325	1670	325	1670	325	1670
326	1680	327	1680	327	1680	327	1680
328	1690	329	1690	329	1690	329	1690
330	1700	331	1700	331	1700	331	1700
332	1710	333	1710	333	1710	333	1710
334	1720	335	1720	335	1720	335	1720
336	1730	337	1730	337	1730	337	1730
338	1740	339	1740	339	1740	33	

39	2 <sup>+</sup>	1 <sup>-</sup>	1 <sup>-</sup>
39	2 <sup>+</sup>	2 <sup>+</sup>	2 <sup>+</sup>
39	1 <sup>+</sup>	weak	weak
39	3 <sup>+</sup>	3 <sup>+</sup>	3 <sup>+</sup>
39	-	3 <sup>+</sup>	3 <sup>+</sup>
39	1 <sup>+</sup>	1 <sup>+</sup>	1 <sup>+</sup>
39	3 <sup>+</sup>	3 <sup>+</sup>	3 <sup>+</sup>
45	3 <sup>+</sup>	3 <sup>+</sup>	3 <sup>+</sup>
45	3 <sup>+</sup>	3 <sup>+</sup>	3 <sup>+</sup>
52	3 <sup>+</sup>	3 <sup>+</sup>	3 <sup>+</sup>
52	3 <sup>+</sup>	3 <sup>+</sup>	3 <sup>+</sup>
56	3 <sup>+</sup>	3 <sup>+</sup>	3 <sup>+</sup>
56	1 <sup>+</sup>	1 <sup>+</sup>	1 <sup>+</sup>
56	3 <sup>+</sup>	2 <sup>+</sup>	2 <sup>+</sup>
56	3 <sup>+</sup>	3 <sup>+</sup>	3 <sup>+</sup>
58	2 <sup>+</sup>	2 <sup>+</sup>	2 <sup>+</sup>
59	2 <sup>+</sup>	1 <sup>+</sup>	1 <sup>+</sup>
68	-	1 <sup>+</sup>	1 <sup>+</sup>
70	3 <sup>+</sup>	3 <sup>+</sup>	2 <sup>+</sup>
70	2 <sup>+</sup>	2 <sup>+</sup>	-
70	1 <sup>+</sup>	1 <sup>+</sup>	1 <sup>+</sup>
70	2 <sup>+</sup> (3 <sup>1</sup> related)	2 <sup>+</sup>	2 <sup>+</sup>
70	1 <sup>+</sup> (1 <sup>8</sup> related)	1 <sup>+</sup>	1 <sup>+</sup>
70	1 <sup>-</sup> (1 <sup>8</sup> related)	1 <sup>-</sup>	1 <sup>-</sup>

\* The digene probe is their type specific probe.

\*\* Cocktail 1 has 500 ng/ml of HPV 16, cocktail 2 has 200 ng/ml HPV 16, and cocktail 3 has 100 ng/ml of HPVs 18,33,35, and 51 plus 200 ng/ml of HPV 31.